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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,451	04/27/2007	Mamoru Sato	10084.0017	2779

22852 7590 04/14/2008

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EXAMINER	
LAO, MARIALOUISA	
ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,451	SATO ET AL.	
	Examiner	Art Unit	
	Louisa Lao	1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,8 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8,10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/07 1/18/08 8/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. There are no entries for the IDS, dated 1/4/07. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

2. Claim 15 is objected to because of the following informalities: the claim should end with a period. Appropriate correction is required. Applicants are further respectfully requested to ascertain that the specification is free of grammatical and typographical errors.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10, 11 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the inhibition or *prevention of* all diseases associated with peptidylarginine deiminases or particularly the prevention of MS or RA or psoriasis by said compounds of formula (II') or salts thereof, as suggested by the breadth of the instant claims. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims. The factors to be considered [in making an enablement rejection] have been summarized as a) the nature of the invention, b) the breadth of the claims, c) the state of the prior art, d)the relative skill of those in the art, e) the predictability or unpredictability of the art, f) the amount of direction or guidance presented, g) the presence or absence of working examples, and h) the quantity of experimentation necessary.

***a) the nature of the invention*:** the instant claims are drawn to the use of said compound of formula (II') or a salt thereof as active ingredient in peptidylarginine deiminase 4 inhibitor in treating MS, RA and psoriasis.

b) *the breadth of the claims*: the claims are extremely broad in that they recite the prevention, which is all encompassing, of diseases for which the compounds are contemplated to be useful to treat because they are associated with peptidylarginine deiminase and therefore may be used to treat *and/or prevent* a plurality of diseases associated with peptidylarginine deiminase. The claims are interpreted to embrace any or *all* diseases associated with peptidylarginine deiminases or particularly the prevention of MS or RA or psoriasis by said compounds of formula (II') or salts thereof. The number of compounds of formula (II') or salts thereof are large and equally the number of diseases. The claims do not recite specific compounds for specific peptidylarginine deiminase activity; the functionality of the compound/s described in the instant claims can be applied to a great many compounds that are known to be useful as treatments, for example, *inter alia,* RA.

c&e) state and predictability of the art. The claimed compound of formula (II') is novel. There is no information in the art regarding their peptidylarginine deiminase activity or their

effectiveness in treating the claimed disorders. The claimed disorders are complex and multi-faceted. The teachings of Chikuma et al. (Ana.Biochem., 285,230-254(2000) *in IDS*) disclose (see abstract) that the their assay of measuring PAD activity may be used to study the physiological role that PAD plays in various tissues, whereupon MBP is elevated in MS patients and that PAD activity may be higher in MS patients. Chikuma et al. teach, however, that this does not support that regulation of PAD will have any effect on the progression or symptomology of a MS patient since reports show that level of PAD activity in the brain white matter of MS patients was not significantly different from that in controls – suggesting that PAD may be activated by certain factors arising under pathophysiological conditions (p 234 last¶).

Kearney et al. *Kinetic Characterization of Protein Arginine Deiminase 4: A Transcriptional Corepressor Implicated in the Onset and Progression of Rheumatoid Arthritis.* Biochemistry (2005), 44(31), 10570-10582, teach that protein arginine deiminase 4 (PAD4) is a Ca2+-dependent enzyme that catalyzes the posttranslational conversion of arginine to citrulline (Arg $\rightarrow$ Cit) in a number of proteins, including histones. While the gene encoding this enzyme has been implicated in the pathophysiology of rheumatoid arthritis (RA), little is known about its mechanism of catalysis, its in vivo role, or its role in the pathophysiology of RA; however, recent reports suggest that this enzyme can act as a transcriptional co-repressor for the estrogen receptor. Kearney et al. teach that specifically, their studies confirm that PAD4 catalyzes the hydrolytic deimination of Arg residues to produce Cit and ammonia. The metal dependence of PAD4 has also been evaluated, and the results indicate that PAD4 activity is highly specific for calcium. Calcium activation of PAD4 catalysis exhibits positive cooperativity with K0.5 values in the mid to high micromolar range. Evidence indicating that calcium binding causes a

conformational change is also presented. Additionally, Kearney et al. show that the steady-state kinetic parameters for a number of histone H4-based peptide substrates and benzoylated Arg derivatives have been determined Km values for these compounds are in the high micromolar to the low millimolar range with kcat values ranging from 2.8 to 6.6 s-1. Kearney et al. show that the ability of PAD4 to catalyze the deimination of methylated Arg residues, and the results indicate that these compounds are *poor PAD4 substrates* ($V/K \leq 31.3$ M-1 s-1) in comparison to other substrates. Kearney et al.'s findings suggest that the *full-length enzyme does not catalyze this reaction in vitro and possibly in vivo either*. (see abstract and summary).

Further, Watanabe et al. *PAD present in various tissues*. Biochimica et Biophysica Acta. 966 (1988) 375-383. teach that there are at least three types of PAD in mammalian tissues, i.e. a muscle type, a hair follicle type and an epidermal type (page 382 last paragraph).

One of ordinary skill in the art at the time of Applicants' invention would interpret that the diseases associated with PAD can encompass any or all of the types of PAD's in mammals.

d)the relative skill of those in the art: the skill is high.

e&f)amount of guidance present and working examples. The instant disclosure provides guidance for the process of the possible PAD4 inhibitory action of the compounds of formula (II') or salts thereof in a schematic diagram (page 39). Applicants have given working example of the inhibition reaction on the PAD4 digestion of the Bz-Arg derivatives (pp 48-49). However, there is no guidance to the prevention of *all* diseases associated with PAD4. There is no guidance to predictably conclude that Applicants can even treat or inhibit multiple sclerosis or rheumatoid arthritis. The instant specification teaches a genetic modification is associated with auto-antibodies in rheumatoid arthritis patients and a supposition that this might suggest involvement

in RA. However, there is no guidance or teaching in the specification to show that an elevation of reaction in a particular disease to be causative or plays any kind of active role. There is no evidence that regulation of PAD4 will have any effect in the course of symptomology of an RA patient. As discussed previously, Kearney et al. confirmed the ability of PAD4 to catalyze the deimination of methylated Arg residues, *however,* and the results indicate that these compounds are *poor PAD4 substrates* (V/K ≤ 31.3 M-1 s-1) in comparison to other substrates. Kearney et al.'s findings suggest that the *full-length enzyme does not catalyze this reaction in vitro and possibly in vivo either*. So, Kearney et al. caution that their study should lay the firm foundation for future development of PAD4 selective inhibitors; since the "methylated Arg residues are poor PAD4 substrates indicates that the methylated Arg residues are unlikely to represent physiologically relevant substrates of the full-length enzyme in the absence of an as yet unknown activating mechanism" (page 10580-82 Conclusion). Further, without further guidance one of ordinary skill in the art will not able to ascertain the myriad of the various types of PAD-associated disorders that the instant compounds of formula (II') or salts thereof, are contemplated to treat. Without further guidance, one of ordinary skill in the art will not be able to ascertain the metes and bounds of the instant application.

g) quantity of experimentation needed. The quantity of experimentation required of a person having ordinary skill in the art could potentially be infinite without further guidance. As stated *supra,* the activity and selectivity of any of the instant compounds, and their effectiveness have to be studied, with extreme caution (see cited references' discussion *supra)*, thus the method of treatment using these compounds follow the same light. Without further guidance, a person of ordinary skill may have to experiment with different types of dosage forms and modes of

administration to determine the method of treatment by which these compounds can be effective by way of the functionality of the compound described in the instant claim(s). All these elements taken into consideration make the experimentation unduly burdensome.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.Cir.1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3, 4, 5, 8 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The compounds are defined by formula (II), (Ia), (Ib),(Ic) and (II') while simultaneously using the nomenclatures of Formula (1), (2), (3), (4) and (5), respectively. It is unclear if these terms are meant to be alternative terms or concurrent terms. Applicants should consistently define the compounds and use the limitations that Applicants intend.

7. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the process steps alluded to by claim 12 in making the compounds of general formula (II'); i.e., claim 12 is a process claim, but there are no process steps.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1, 3, 4, 5, 8 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kearney et al. *Kinetic Characterization of Protein Arginine Deiminase 4: A Transcriptional Corepressor Implicated in the Onset and Progression of Rheumatoid Arthritis.* Biochemistry (2005), 44(31), 10570-10582.

10. The instant claims are drawn to a compound of the general formula (II), (Ia), (Ib), (Ic) and (II') or salt thereof; the method of making said compound of formula (II') or a salt thereof. Claims 10 and 11 include an intended use of said compound of formula (II') or a salt thereof as active ingredient in peptidylarginine deiminase 4 inhibitor in treating MS, RA and psoriasis. The intended use of claims 10 and 11 does not appear to alter the structure of the compound claimed.

11. Kearney et al. teach the synthesis of dimethyl-benzoyl-L-arginine ethyl ester in Scheme I, page 10578.

12. Kearney et al. anticipates the instant claims when not all R^1, R2, R^3 are all H; or alternatively, "provided that at least one of R^1, R^2 , R^3 does not represent H"; R^4 = substituted N and R^5 = substituted -COOH.

13. No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MLouisa Lao whose telephone number is 571-272-9930. The examiner can normally be reached on Mondays to Thursdays from 8:00am to 8:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne

Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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